CLINICAL PROFILE OF SYSTEMIC SCLEROSIS

Dissertation submitted for

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CERTIFICATE

This is to certify that the dissertation titled **"CLINICAL PROFILE OF SYSTEMIC SCLEROSIS"** is the bonafide original work of **DR.K.SUBRAMANIYAN** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in MARCH 2007. The Period of study was from October 2005 and September 2006.

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DECLARATION

I, **DR.K.SUBRAMANIYAN,** solemnly declare that dissertation titled **"CLINICAL PROFILE OF SYSTEMIC SCLEROSIS"** is a bonafide work done by me at Government Stanley Medical College and Hospital from 2005 - 2006 under the guidance and supervision of my unit chief **Prof.Dr. S.NATARAJAN, M.D.,** Professor and Head of Department of Medicine, Government Stanley Medical College and Hospital, Chennai.

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – March 2007.**

Place : Chennai.

Date :

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INTRODUCTION

SYSTEMIC SCLEROSIS (SSc)

Systemic sclerosis is a chronic multisystem disorder of unknown etiology characterized clinically by thickening of the skin caused by accumulation of collagen and by structural and functional abnormalities of visceral organs including the gastro intestinal tract, lungs, heart and kidneys[1].

Systemic sclerosis is often of tragic consequence to patients. Survival is determined by the severity of visceral disease, especially involving the lungs, heart and/or kidneys.

Earlier reports indicate that SSc rare in Asian Indian, Chinese and Malaysian[8,9].

Contrary to this, later reports from India definitely have shown SSc is not uncommon in India, with a distinctly different clinical picture compared to that observed in the Western Countries[10,11,12,13,14].

AIMS OF THE STUDY

1. To study the clinical spectrum of patients presenting with Systemic Sclerosis (SSc)

2. To evaluate the internal organ involvement

SYSTEMIC SCLEROSIS

HISTORICAL REVIEW[2]

The first convincing description was in 1753 by Carlo Curzio. He described a 17-year-old patient as having 'extensive tension and hardness of skin all over her body'. Curzio managed the case with bloodletting, warm milk and 'small doses of quick silver'. However, it was only in the mid 19th century that scleroderma was established as a clinical entity and given its current name. In reviewing the described cases to date, Glintrac, in 1847, ascribed the name sclerodermie. Maurice Raynaud described Raynaud's phenomenon in 1865 and Jonathan Hutchinson reported a case with Raynaud's phenomenon who had definite features of scleroderma in 1883. William Osler referred to the systemic nature of the disease in his 1894 textbook of medicine (patients were 'apt to succumb to pulmonary complaints or to nephritis') and Klemperer, Pollack and Baehr, in 1942, proposed that scleroderma should be considered as a 'systemic disease of the connective tissue. It was not until 1945, however, that Goetz proposed the term progressive systemic sclerosis to emphasize the degree of visceral disease.

In 1964, Winter Bauer described the CRST syndrome (now the CREST syndrome of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia), although it was first described in 1910 and originally termed Thiberge – Weissenbach syndrome after the presenting physicians. In 1969 a major pathologic review delineated the widespread fibrotic and vascular disease of scleroderma. Clinical and pathologic surveys of patients with scleroderma followed, giving new insight into the clinical features, risk factors, pathogenesis of fibrosis and associations of scleroderma with the immune response. In the last decade, there has been remarkable progress in understanding the molecular mechanisms of fibrosis, micro vascular injury and the autoimmune process in this rare disease.

REVIEW OF THE LITERATURE

SYSTEMIC SCLEROSIS[2] (SSc)

Systemic sclerosis is a disfiguring multi system disease that may alter every aspect of an individual's life. It includes a broad spectrum of disease with varying degree of organ involvement. This subset of patients exist with unique clinical features and distinct outcomes.

Raynaud's phenomenon, the manifestation of perturbation of the terminal arteries of the circulatory system. This outward manifestation of vascular disease is a marker of tissue ischemia that is linked to a progressive fibrosing process in specific target organs; the skin, lung, heart, gastrointestinal tract and kidney.

In the diffuse cutaneous variant systemic sclerosis, fibrosis of skin and other organs is widespread and potentially life threatening. In the limited form of systemic sclerosis the skin fibrosis is limited to the fingers and/or distal limbs with a more benign and indolent disease course. Limited cutaneous systemic sclerosis is less likely to be associated with serious internal organ involvement.

CLASSIFICATION OF SYSTEMIC SCLEROSIS (SCLERODERMA)[3]

DIFFUSE CUTANEOUS SCLERODERMA

Skin thickening present on the trunk in addition to the face, proximal and distal extremities.

LIMITED CUTANEOUS SCLERODERMA

Skin thickening limited to sites distal to the elbow and knee but also involving face and neck. This subset frequently has features of the **CREST Syndrome (C = Calcinosis; R = Raynaud's phenomenon; E = Esophageal dysmotility: S = Sclerodactyly; T = Telangiectasia)**

SINE SCLERODERMA

Characteristic internal organ manifestation, vascular and serological abnormalities but without clinically detectable skin change.

OVERLAP SYNDROME

Any of the three previous classification occurring concomitantly with a diagnosis of systemic lupus erythematosus (SLE) inflammatory muscle disease (or) Rheumatoid Arthritis.

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

Raynaud's phenomenon with clinical and/or serologic features of systemic sclerosis (digital ulceration, abnormal nail fold capillary loops, serum anticentromere antibody, finger edema) but without skin thickening and without internal organ abnormalities of systemic sclerosis.

CRITERIA FOR CLASSIFICATION[3,42]

The American College of Rheumatology (former American Rheumatism Association) has defined criteria that are 97% sensitive and 98% specific for SSc as follows:

Major Criteria

Sclerodermatous skin change in any location

Proximal to the Metacarpophalangeal joints

Minor criteria

- Sclerodactyly
- Digital pitting scars of finger tips (or)
- Loss of digital finger pad substance and
- Bibasillar pulmonary fibrosis

Diagnosis

One Major criteria (or) two or three minor criteria

INCIDENCE AND EPIDEMIOLOGY

The incidence of systemic sclerosis derived from modern, well designed studies is between 18 and 20 individuals per millions of population per year[4,5].

SSc is found in all geographic areas and all racial groups, although blacks may be at moderately increased risk[6,7].

SSc affects all age groups onset of disease between the ages of 30 and 50 years[4,5,6,7].

SSc three to four times more common in women than in men[6,7].

Earlier reports indicate that SSc rare in Asian Indian, Chinese and Malaysian[8,9]. Contrary to this, later reports from India have definitely shown SSc is not uncommon and occurs with a distinctly different clinical picture compared to that observed in the Western countries[10,11,12,13,14].

Occupational silica or metal dust exposure has been linked with occurrence of SSc[15]. Although the disease is clinically indistinguishable from idiopathic systemic sclerosis, genomic difference in both class II HLA and tumor necrosis factor (TNF) alleles suggest a difference in the mechanism of disease[15]. Reports of the familial occurrence of systemic sclerosis are rare. It is more common than would be expected by chance alone. The concordance of SSc in identical twins is 5 – 9 percent roughly 300 fold that of chance alone.

A genetic contribution to disease is likely. Studies of HLA phenotypes by serologic technique have suggested linkage of disease with HLA-A1, B8, DR3 haplotype or with DR3 DR52[16,17].

Major histocompatibility complex analysis at the DNA level has revealed strong association with C4 AQO and DQ A2. Furthermore, there are strong association of class II major histocompatibility complex alleles with serologically and clinically defined subjects of disease[18].

First degree relatives of patients with SSc are mere likely to have serum antinuclear antibody[19].

ENVIRONMENTAL FACTORS

Environmental factors induce SSc-like diseases. Several reports describe chemical compounds within our environment and their ability to induce SSc-like diseases upon exposure (Table)[20,21,22]. These substances can induce SSc-like diseases that can be distinguished from SSc by the following features:

- Type of skin manifestation, in particular acrosclerosis, circumscribed and generalized morphea, fibrotic nodules, joint contractures.
- Visceral involvement due to toxic damage of the liver, kidney, nervous system and muscles, angiosarcoma of the liver.
- Laboratory findings of partial thrombocytopenia, and absence of autoantibodies.
- Cessation or reversibility of the disease process after early discontinuation of the exposure.

Table : Environmental substances inducing scleroderma-like disease and their exposure

Substances	Exposure
Chemical compounds Plastics (monomers) (vinyl chloride epoxy resins)	Cleaners of vinyl chloride reactors Construction workers
Solvents (Chlorinated)aliphatic and aromatic hydrocarbons	Workers in dry cleaning chemical industry, pump attendants
Pesticides	Workers in agriculture, gardeners, chemical industry, patients (iatrogen, abuse)
Drugs Bleomycin Pentazocine Ethoxisuximide Penicillamine	Patients
Other Paraffin (silicone*) Aniline contaminated rapeseed oil, salad oil (toxic oil syndrome), L-tryptophan	Patients (breast augmentation*) Consumers
Minerals Silica	Miners, foundry workers/foremen, quarrymen, sandblaster, sandstone sculptors, glass grinders, cast polishers, dental mechanics

PATHOPHYSIOLOGY

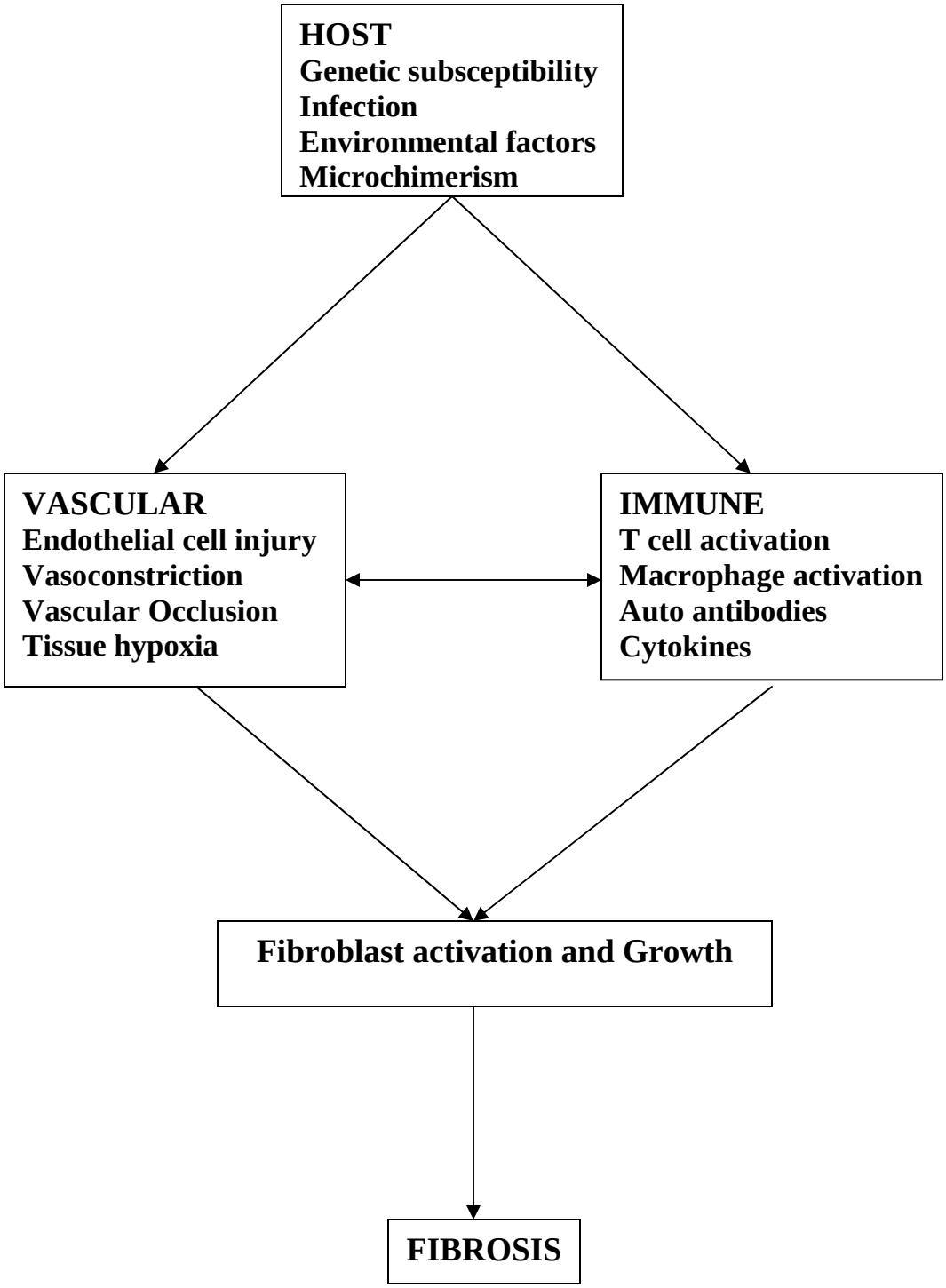
Excessive collagen deposition causes skin and internal organ changes. Many factors, including environmental factors can lead to immunologic system disturbances and vascular changes. Endothelial alterations may lead to cascade of stimulatory changes that involve many cells, including fibroblasts, T lymhocytes, macrophages and mast cells. In turn, the activated cells secrete a variety of substances, including cytokines and their soluble receptors and enzymes and their inhibitors. These substances lead to changes in the extra cellular matrix compounds, including fibronectin; proteoglycans and collagen types I, III, V and VII. Increased collagen deposition in tissues is a characteristic feature of SSc. Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues.

Fibrosis can be caused by profibrotic cytokines, including transforming growth factor-beta (TGF-beta), interleukin-4 (IL-4), platelet-derived growth factor (PDGF), and connective tissue growth factor. The vasculopathy may be linked to TGF-beta and PDGF, while the diminution of lesional cutaneous blood vessels can be attributed to ant endothelial cell auto antibodies. The activation of the immune system is of paramount importance in the pathogenesis of SSc. Antigen-activated Tcells, infiltrate early, infiltrate the skin and produce the profibrotic cytokine IL-4. B cells may contribute to fibrosis, as deficiency of CD 19 B-cell transduction molecule, results in decreased fibrosis in animal models.

Different factors, including genetic, environment, vascular, autoimmunologic and microchimeric factors are involved in SSc pathogenesis. One theory states that antigens from the human leukocyte antigen (HLA) histocompatability complex, including HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52 and HLA-DQB2 are involved. Some data suggest that apoptosis and the generation of free radicals may be involved in the pathogenesis of SSc.

In SSc, affected organs and systems include the skin, lungs, heart, digestive system, kidneys, muscles, joints and nervous system.

ALGORITHM FOR THE MULTIFACTORIAL PATHOGENIC MECHANISMS OF SYSTEMIC SCLEROSIS[1]



CLINICAL FEATURES

RAYNAUD's PHENOMENON [1]

Raynaud's phenomenon, the initial symptom of SSc in the majority of patients, is a clinical expression of the abnormal regulation of blood flow resulting from vascular injury. Injury to endothelial cells and basal lamina occurs early and is followed by proliferation of intima and smooth muscle cells with deposition of matrix and perivascular fibrosis leading to narrowing of the lumen and eventual obliteration of the vessel.

Raynaud's phenomenon, which is defined as episodic vasoconstriction of small arteries and arterioles of fingers, toes, and some times tip of nose and earlobes. Patients experience pallor and/or cyanosis following by rubor on rewarming. Pollar and or cyanosis are usually associated with coldness and numbness of fingers and toes, and rubor with pain and tingling. History of Digit pallor most reliable symptom for presence of Raynaud's phenomen.

Raynaud's phenomenon may precede skin changes by several months or even years in those patients who subsequently develop limited cutaneous form of SSc. In diffuse cutaneous SSc skin changes are seen typically within a year of onset of Raynaud's phenomenon.

After 2 or more years of Raynaud's phenomenon, few patients who have this as their only symptom well subsequently develop SSc.

SKIN MANIFESTATIONS[2]

The skin disease of scleroderma follows a course characterized by three phases. An inflammatory edematous phase, an endurative phase and an atrophic phase.

Three stages do not have distinct beginning and ending there is high degree of variability in the duration of inflammatory signs and in the severity and extent of the skin involvement.

In the Edematous phase, patient experiences puffiness, swelling and a sense of decreased flexibility of the skin especially in forearm, hands and degits as well as feet. Fingers appear puffy with moon like fullness of finger tips and loss of digital creases, loss of finger pad and tapering of finger due to finger tip ischemia. This process may be last for months duration this time induration and skin thickening evident. After inflammatory phase there is long course of progressive fibrosis of skin in diffuse cutaneous scleroderma and later atrophic phase sets in with loosening of skin.

DIFFUSE CUTANEOUS SCLERODERMA

Characterized by tightening and thickening of skin that can involve extremities, chest, neck, face and abdomen. Areas of mid back usually spared. Skin of the abdomen usually diffusely thickened. Patients with diffuse skin disease a pulling, tight serration around upper chest and shoulder girdle a common complaint. Anterior neck may develop horizontal fold of skin called the scleroderma ‘neck sign’.

Pigmentary changes of the skin occur during the edematous and fibrotic stage but these changes vary in intensity and distribution. Depigmentation occurs especially in scalp, eyebrows, upper back, chest, hand. This vitiligo pattern gives the skin a 'salt and pepper' appearance because of perifollicular sparing of pigment loss.

Some patients develop diffuse tanning of skin. Some have scattered patches of hyperpigmentation particularly over pressure points.

In the late stage of scleroderma, the skin becomes atrophic and thinned tethering secondary to fibrotic tissue binding to underlying structure.

FACE[2]

Face becomes expressionless because of reduced capacity to smile or more eyelids or cheeks. The opened mouth becomes circular with a remarkable reduction in maximum oral aperture (Microstomia). Vertical lines or furrowing of the skin around the lips gives a pursed lip appearance. The tight perioral skin sometimes makes the frontal teeth appear more prominent. The nose becomes pinched and facial areas smooth so that face has a mouse like appearance (Mauskopf).

LIMITED CUATANEOUS SCLERODERMA

Skin thickening limited to sites distal to elbow and knee but also involving face and neck. This subset frequently has features of the CREST =

(C = Calcinosis; R = Raynaud's phenomenon; E = Esophageal dysmotility:

S = Sclerodactyly; T = Telangiectasia)

LOCALIZED SCLERODERMA

Occurs most often in children and young women but can affect any age group.

Two forms 1. Morphea

2. Linear scleroderma

Morphea - Single or multiple plagues of skin induration

Linear scleroderma - Involves extremity or face.

en coup de sabre:

Linear scleroderma of one side of forehead and scalp produces a disfiguration because it resembles a wound from a sword. It may be associated with hemiatrophy of the same side of face.

MUSCULOSKELTAL FEATURES

More than half the patients with SSc have arthralgia and arthritis. A symmetric polyarthritis resembling rheumatoid arthritis may be seen. Muscle weakness is usually present in patients with severe skin involvement most cases is due to disuse atrophy. A few patients may develop myositis characterized by proximal muscle weakness and muscle enzyme elevation are identical to

polymyositis (over lap syndrome). In addition to terminal phalanges, resorption of bone may invite rib clavicle and angle of mandible.

GASTROINTESTINAL FEATURES

The Gastrointestinal involvement is more common in SSc. Symptoms attributable to esophageal involvement are present in more than 50% of patients[23,24].

Symptoms include Dysphagia, Regurgitation of gastric contents, epigastric burn. Dysphagia particularly of solid foods may occur because of loss of esophageal motility due to neuromuscular dysfunction. Manometry or cineradiography reveals decreased amplitude or disappearance of peristaltic waves in the lower two thirds of the esophagus.

Regurgitation and epigastric burn are due to reduced tone of the gastroesophageal sphincter and to dilatation of the distal esophagus. Peptic esophagitis frequently occurs and may lead to strictures and narrowing of the lower esophagus. Barrett's metaplasia may develop, but transition to adenocarcinoma is uncommon[25]. Barium studies show dilatation, atony and delayed emptying.

Involvement of stomach present clinically as early satiety. Vascular ectasia may develop in the stomach and intestine. These dilated submucosal capillaries in the stomach appear an endoscopy as broad stripes – Watermelon stomach is a cause of bleed in SSc.

Peristalitic abnormalities may delay gastric emptying and may affect motility of small and large intestines leading to pseudoobstruction and malabsorption due to bacterial overgrowth. In addition diverticular ulceration, stenosis, chronic obstipation, mega colon and rectal prolapse have been described.

Liver is rarely involved primarily in SSc[26]**.** primary biliary cirrhosis can occur as an overlap syndrome.

PULMONARY INVOLVEMENT

Pulmonary involvement occurs in at least two thirds of SSc patients and now the leading cause of death in SSc.

The most common symptom is exertional dyspnea, after accompanied by a dry cough, non productive cough.

Physical findings include fine early inspiratory 'Velero-like' crackles at the lung base in case of interstitial lung disease.

The most sensitive method for detecting early lung disease in SSc is to perform pulmonary function testing.

Mild changes in function can be detected before any symptom develop. The most common changes of pulmonary function testing are a reduced diffusion capacity (D_LCO) or a reduction in lung volumes (forced vital capacity, FV) typical of a restrictive ventilatory defect with associated reduction in gas exchange. Chest (X ray) film may show pattern of linear densities, mottling and honeycombing, involving most prominently to lower $2/3^{rds}$ of lung.

Early interstitial pulmonary disease can be detected by high resolution computed tomography (HRCT) and Broncho Alveolar Large (BAL). Active Inflamatory alveolitis gives a ground glan appearance of HRCT. The recovery by Broncho Alveolar Large of increased number of cells mostly alveolar macrophages accompanied by neutrophils or esenophils is evidence of alveolitis.

Individuals with limited systemic sclerosis may also develop interstitial lung disease but also have a risk for primary pulmonary hypertension, a complication most typical of longstanding disease.

HEART

Cardiac involvement is often present, but rarely significant clinically. Even dyspnea and retrosternal pain are attributed mainly to other organs such as lung or esophagus. In addition, syncope and angina pectoris may be caused by either endothelial damage of small coronary arteries or myocardial fibrosis due to other basic diseases. It is hard to prove the specificity of this involvement due to SSc itself. The prevalence reported in the literature depends upon the diagnostic methods chosen. Myocardial perfusion scintigraphy, ventriculography and echocardiography are the most sensitive techniques. Clinically manifested forms have been described in 20-25 % with a 70% mortality after 5 years. However, autopsy revealed alterations such as myocardial fibrosis and pericardial effusion in 30-80% of patients[27,28]. Myocardial fibrosis occurs as patchy or diffuse forms. Repeated episodes of ischemia and reperfusion lead to the destruction of the myocardium and replacement by connective tissue[29]. In echo cardiographic studies of 80 SSc patients, hypokinetic alterations of the left ventricle were found. Echo cardiographic abnormalities such as conduction system disturbances (27%), signs of infarction (13.8%), and non specific ST and T wave changes (13.8%) were observed[30].

KIDNEY

Affection of the kidney has the worst prognosis and highest mortality of all internal organs involved. Clinically 10 - 40% are affected, but by autopsy, the figure is 80%[33]. Patients with diffuse skin involvement carry a high risk of an acute renal crisis characterized by malignant arterial hypertension with headache, vision disturbances, cramps, left ventricular hypertrophy and retinopathy. It generally manifests itself within the first 4 years. However, the chronic form develops slowly over years and leads, in 50% of affects patients, to a moderate reduction of kidney function, often clinically in apparent. Diagnostic criteria are proteinuria (< 1 g/24 h), azotemia (blood urea nitrogen (BUN) >25 mg/100 ml), arterial hypertension (> 140/90 mmHg) and reduction of the glomerular filtration rate. Factors predictive to renal crisis are list in table[34].

Table : Factors predictive to renal crisis

- Diffuse skin involvement
- Rapid progression of skin thickening
- Disease course < 4 years
- Anti-RNA-polymerase III antibodies
- Newly manifested anaemia
- Newly manifested cardiac involvement
- - Pericardial effusion
- - Heart insufficieny
- Preceded high-dose corticoid therapy

The pathogenetic events are not completely understood. The primary event seems to be the damage endothelial cells with thickening and proliferation of the intima with deposits of glycoproteins and mucopolysaccharides in the interlobular and small arcuade arteries. These changes lead to narrowing or even obliteration of vessel lumina and ultimately to infarction of glomeruli and tubuli. This is followed by platelet aggregation, adhesion and liberation growth factors.

Sjögren Syndrome

Sjögren Syndrome is defined as an inflammatory disorder of salivary glands often characterized by circulating antibodies to Ro (SSA) and La (SSB) antigen. Depending on the diagnostic criteria used it occurs in 5 to 90% of SSc patients, in particular those with limited disease[35,36].

NERVES

Neurological manifestations include peripheral neuropathy with reduction in the conduction velocity and patients often show a prolonged response to local anaesthesia[37]. Trigeminal neuralgia is found in about 4% of patients; carpal tunnel syndrome occurs in 3% of patients[38,39].

HEMATOLOGICAL ABNORMALITIES

Hematological abnormalities are mostly related to renal disease, microangiopathic hemolytic anaemia or from bleeding gastrointestinal teleangiectasias[40].

PREGNANCY

Although pregnancies are less frequent in SSc, women can safely have healthy deliveries. Steen has prospectively observed 91 pregnancies during a 10-year period[41]. No increase in the frequency of miscarriage was found except in those with long-standing diffuse scleroderma. In 29% of pregnancies, preterm birth occurred and all but one of the infants survived. While Raynaud's phenomenon improved during pregnancy, esophageal reflux became worse. After delivery some women with diffuse SSc had increased skin thickening. In early diffuse SSc three patients suffered from renal crisis. Therefore, patients with early diffuse SSc should wait until their disease stabilizes before becoming pregnant. High risk pregnancy management is required.

INVESTIGATIONS

Lab findings (SSc)

- ♣ Erythrocyte sedimentation Rate is increased
- ♣ Hyper gammaglobulinaemia
- ♣ Microangiopathic Haemolytic anemia
- ♣ Increased creatine phosphokinase levels in patients with muscle involvement.
- ♣ Increased urea and creatine levels in patients with kidney involvement
- ♣ Proteinuria (more than 200 mg/24 hours) in renal involvement

Immunological

1. CRP - Increased
2. Rheumatoid factor – low titre – positive in 25%
3. ANA
4. Antipoisomerase antinuclear, anticentromere – Positive in limited cutaneous lesions.
5. Anti Scl – 70 – positive 40% for diffuse cutaneous lesions.

SKIN BIOPSY

Epidermal skin appendages atrophy, and collagen fibres in the retricular dermis appear broad and hyalinized. A loss of space between collagen bundles is noted. Mononuclear cells, mostly T cells form a variable perivascular infiltrate in the deep dermis and subcutis. Later sclerotic changes predominate, the number of adnexal structures is reduced and loss of peri adnexal fat is noted.

MATERIALS AND METHODS

Patients who attended the Rheumatology department from October 2005 to September 2006 were taken up for the study.

Systemic sclerosis was diagnosed in 25 patients as per the American College of Rheumatology (formerly American Rheumatism Association Scleroderma criteria cooperative study)[42] criteria.

Major Criteria

Sclerodermatous skin change in any location proximal to the Metacarpophalangeal joints

Minor criteria

- Sclerodactyly
- Digital pitting scars of finger tips (or)
- Loss of digital finger pad substance and
- Bibasillar pulmonary fibrosis

Diagnosis

One Major criteria (or) two or three minor criteria

The sensitivity of these criteria was 97% and the specificity 98% by applying this American College of Rheumatology Criteria

The all 25 patients were analyzed from clinical, Biochemical, Immunological and radiological parameters.

- Detailed clinical examination has done according to the proforma (attached).
- Biochemical investigations done for all the patients (complete blood count, Renal Function Test, Liver Function Test).
- Immunological investigations including:
  - Rheumatoid factor
  - Anti Nuclear Antibody
  - CRP (Creactic Protein) all done.
- Skin biopsy was done for 23 patients.
- Radiological investigations consists of X ray chest and X ray hand.
- Computed tomography chest was done for those who presented with Respiratory Symptoms.

- ECG (Electrocardiography) done for all patients.
- Echocardiography was done who presented with cardiovascular symptoms.
- Pulmonary Function Test was carried out for those who presented with Respiratory symptoms,
- Ba Swallow, upper gastrointestinal endoscopy done for all the patients who attributed with symptoms of gastrointestinal tract.
- Antitopoisomerase1 (anti Scl-70) not done because of lack of facility.

OBSERVATION AND INTERPRETATION

AGE AND SEX PRESENTATION

Among 25 patients 2 were males and 23 were females (M : F ration 1 : 11.5).

The youngest was = 20 years

The oldest was = 60 years

Table 1 Analysis of Age and Sex presentation

Age	Male	Female	Total	%
20 – 30	**0**	**4**	**4**	**16**
31 – 40	**1**	**7**	**8**	**32**
41 – 50	**1**	**8**	**9**	**36**
51 – 60	**0**	**4**	**4**	**16**

The mean age was = 40 years

The highest incidence seen in

3^{rd} decade 32% and

4^{th} decade 36%

SYMPTOM ANALYSIS

The initial presentation was skin symptoms in 13 patients (52%). Arthralgia in 10 patients (40%) and Raynaud's phenomenon in 2 patients (8%) and visceral symptoms (Dyspnoea on exertion) in one patient (4%).

SYMPTOM ANALAYSIS – INITIAL PRESENTATION

Symptoms	No.of patients	%
Skin	**13**	**52%**
Arthralgia	**10**	**40%**
Raynaud's Phenomenon	**2**	**8%**
Visceral symptoms	**1**	**4%**

Majority of patients had their symptoms between 30 – 50 years of age.

CUMULATIVE MANIFESTATIONS

Symptom Analysis

Symptoms	No.of patients	%	South Indian Study[43,44,45]
Skin	25/25	100%	98.9%
Joint	20/25	80%	66.7%
Raynaud's phenomenon	7/25	28%	28.2%
Visceral manifestation	7/25	28%	

- 25 patients had skin changes (100%)
- 20 patients had Arthralgia/Arthritis (80%)
- 7 patients had Raynaud's phenomenon (28%)
- 7 patients had visceral symptoms (28%)

ANALYSIS OF CLINICAL MANIFESTATIONS

SKIN INVOLVEMENT (CUTANEOUS)

Clinical features	No. of patients	%	South Indian Study[43,44,45]	North Indian Study[12]	West Indian Study[14]	Western Country[46]
1. Limited cutaneous						
a. Sclerodactyly	10	40	33.3	10.3	14.2	0
b. Pigmentary changes (Hyper Pigmentation & Pepper salt pigmentation)	17	68	73.1	36.8	76.2	30.5
2. Calcinosis	0	0	1.1	2.3	41	8.9
3. Ulceration, Stellate scars	15	60	60	53	--	--
4. Telangiectasia	0	0	1.1	2.3	41	8.9
5. Resorption Hand	1	4	13.2	NA	NA	NA
6. CREST	0	0	1.1	0	4	--
7. Vasculopathy ulcer	1	4	4.1	--	2	--
8. Diffuse cutaneous	1	4	21.4	62.1	NA	5.4

- **Skin involvement was seen in all patients.**
- **Pigmentary changes were more common (68%).**
- **Sclerodactyly – next common manifestation (40%).**

VASOSPASTIC CHANGES (Raynaud's Phenomenon)

Features	No.of patients	%	South Indian Study[43,44,45]	North Indian Study[12]	West Indian Study[14]	Western Country[46]
Vasospastic changes	**7/25**	**28%**	**46.9**	**97.7**	**83.3**	**94.6**
Severity						
Mild	**3/25**	**12**	--	--	--	--
Severe	**4/25**	**16**				
Involvement						
Unilateral						
Bilateral	**3/25**	**12**	**14**	**37.8**	--	--
	4/25	**16**	**23**	**62.2**		

Vasospastic changes were present in 7 patients. This is comparatively less than other studies.

JOINT INVOLVEMENT

Joint involvement Feataures	No.of patients	%	South Indian Study[43,44,45]	North Indian Study[12]	West Indian Study[14]	Western Country[46]
Minor Joints	**13/25**	**52**	**63.5**	**--**	**--**	**41%**
Major joints	**7/25**	**28**	**36.5**	**--**	**--**	
Deformity	**5/25**	**20**	**13.13**	**50**	**--**	**--**

Joint manifestation were seen in 20 patients (80%).

Internal Organ Manifestations

Gastro Intestinal Tract Manifestations

Out of 25 patients 18 patients presented with Dysphagia and Regurgitation. All the sympatomatic patients underwent Ba Swallow and upper gastro Intestinal Endoscopy.

Symptoms	No. of patients	%	Ba Swallow	Upper gastro Intestinal Endoscopy
Dysphagia	**12/25**	**48%**	**Dilated esophagus**	**Normal**
Regurgitation	**6/25**	**24%**	**Normal**	**Gastro esophageal Reflux disease**

Patients presented with Dysphagia showed dilated esophagus in Barium Swallow studies (48%).

Patients presented with Regurgitation showed gastro esophageal reflux disease on upper gastro intestinal endoscopy (24%).

RESPIRATORY SYSTEM

Out of 25 patients 4 had symptom of Respiratory system in the form of Exertional Dyspnea for which all patients were investigated with chest x ray, pulmonary function test and CT chest.

Patient No.	Symptom	Chest X ray	P.F.T.	CT Chest
Patient No.1	**Exertional dyspnea**	**B/L basal Haziness**	**Mod to severe restrictive air way disease**	**Interstitial lung disease**
Patient No.2	**Exertional dyspnea**	**B/L basal Haziness**	**Mod to severe restrictive air way disease**	**Interstitial lung disease**
Patient No.3	**Exertional dyspnea**	**Normal study**	**Mild to moderate restrictive air way disease**	**Normal study**
Patient No.4	**Exertional dyspnea**	**Normal study**	**Mild to moderate restrictive air way disease**	**Normal study**

Out of 4 patients who had symptoms of Exertional Dyspnea, X ray chest was normal for 2 patients.

X ray chest : showed basal (B/L) Haziness for another 2 patients.

PFT : showed mild to moderate Restriction air way disease for 2 patients who had X ray normal.

PIT : showed moderate to severe restriction airway disease for 2 patients who had x ray B/l basal Haziness.

CT Chest : showed Interstitial lung disease for 2 patients who had X ray findings and PFT showed moderate to severe restriction air way disease. Another 2 patients CT normal study.

CARDIO VASACULAR MANIFESTATIONS

Out of 25 patients symptoms attribute to the Cardiovascular system were present in 4 patients (16%) for which they were evaluated for cardiac involvement.

No.of patients	Symptoms	X Ray chest	ECG	Echo
Patient No.1	**Chest pain Dyspnea on exertion**	**Enlarged cardiac silhovette sign**	**Low voltage QRS complex and increase of T waves**	**Moderate pericardial effusion**
Patient No.2	**Chest pain and palpitation**	**Normal**	**Normal**	**Mitral Valve prolapse disease**
Patient No.3	**Chest pain Dyspnea on exertion**	**Enlarged cardiac silhovette sign**	**Increase of T waves**	**Mild to moderate pericardial effusion**
Patient No.4	**Dyspnea on exertion**	**Basal Haziness**	**Normal**	**Pulmonary Hypertension secondary to ILD**

RENAL SYSTEM

Out of 25 patients Renal involvement was absent in all patients. Renal involvement was screened in the form of Proteinuria (more than 200 mg/24 hrs) and Hypertension and renal function tests.

Acute onset of malignant hypertension followed by rapidly progressive renal insufficiency is termed as Scleroderma renal crisis which is lkow in Indian patients[47].

Screeing for Renal Involvement

No.of patients	%	Renal Function Test	24 Hours proteinuria	B.P.
25	0/25	Normal	Normal	Normal

INTERNAL ORGAN INVOLVEMENT

	No.of patients	%	South Indian Study[43,44,45]	North Indian Study[12]	West Indian Study[14]	Western Country[46]
Gastro Intestinal	18/25	72	40.8	50.5	12	42
Respiratory	4/25	16	19.4	57.4	12	70
Cardio vascular	4/25	16	9	11	3	20.2
Renal	0/25	0	10	19.5	2	14.9

INVESTIGATIONS

Sl. No.	Investigations	No.of patients	%	South Indian study	North Indian Study	Western study
1.	Hb < 10 gm%	4/25	16%	14.75	11.1	20.9
2.	ESR > 20 mm/hr	17/25	68%	70.5	75.3	70.0
3.	Proteinuria (> 200 mg/24 hrs)	0/25	0%	10.2		
	Rheumatoid Factor	4/25	16%	16.4	12	22
4.	ANA	9/25	56%	51.85	66.6	40.90
5.	CRP	8/25	40%	40.48	--	--
6.	Skin Biopsy	23/25	92%	97.44%	80%	--

1. **Normocytic Normochromic anemia in 16% [43,44,45].**
2. **ANA in low titre detected in 56%.**
3. **Rheumatoid Factor was positive 16%.**
4. **CRP was positive in 40%.**

RESULTS

- There were 2 males and 23 females giving a sex ratio of (1 : 11.5)
- The age ranged from 20 – 60 years with a mean age of 40 years.
- The highest incidence seen in 3rd decade (32%) 8 patients and 4th decade (38%) 9 patients.
- The initial presentation was skin manifestation (52%) Arthralgia (40%) Raynaud's (8%) Viseral symptom (4%).
- Cumulative manifestations include skin (Cutaneous) 100%, Diffuse skin
- Involvement seen in (4%), Arthralgia (80%).
- No one presented with fully developed CREST syndrome.
- Calinosis Nil
- Reynaud's 28%
- Esophageal dysmotility 48%
- Sclerodactyly 40%
- Pigmentary lesions in the form of Hyperpigmentation and pepper salt
- Pigmentation in (68%).
- Joint involvement in the form of arthralgia was seen in 80%.
- Gastro Intestinal system was involved in 72%.
- Respiratory system was involved in 16%.
- Cardiovascular system was involved in 16%.
- Renal system was not involved even in one case.

Lab Results showed

- Increased erythrocyte sedimentation rate in 68%[43,44,45].
- ANA in low titre detected in 56%[43,44,45].
- Rhematoid factor was postive in 16%.
- CRP was positive in 40%.

Out of 25 patients

- Only one patient was having diffuse SSc.
- Two patients were having undifferentiated SSc. (Having only Raynaud's Phenomenon + skin changes + serology positive)
- 22 patients were limited cutaneous SSc.

DISCUSSION

The various clinical features of systemic sclerosis of 25 patients have been analyzed in this study. The results are compared with previous South Indian Study[43,44,45], North Indian Study[12], West Indian Study[14] and Western country[46] study.

Out of 25 patients studied there were 2 males and 23 females with a sex ratio of 1 : 11.5 with female preponderance[6,7]. Similar to universal picture the mean age of onset in this study was 40 years[4,5,6,7] similar to other studies. The peak age of onset occurred in 3rd and 4th decade in this study this is also comparable with other studies[4,5,6,7]. It was very similar to other studies.

Raynaud's phenomenon was the most common presenting symptom in North Indian[12], West Indian[13] and Western Country study[46]. But in this study and South Indian study Raynaud's phenomenon was low incidence[43,44,45]. In this study Raynaud's presentation was 28%. The lower incidence of Raynaud's in this study is probably due to hot climate prevailing in South India[43,44,45].

Vascular involvement in the form of vasculitic ulcers seen in 1 patient. One patient had resorption of terminal phanges of fingers in radiograph of hands probably due to ischemia of the digits[43,44,45].

In this study skin (cutaneous lesions) (100%) and arthralgia (80%) were the most common presenting manifestations which is similar to previous South Indian study and other studies[43,44,45].

One of the patient in this study had diffuse skin involvement and internal organ involvement affecting lungs as Interstitial lung disease and pericardial effusion.

CREST syndrome was not noticed in any patient. Similar to South Indian Study[43,44,45].

Pigmentary changes were present in as high as 68% and this is comparable with West Indian study where the incidence of pigmentation was 76.2% and this may be because of Geographical location of these two zones which are closer to equator.

Sclerodactyly (40%) was seen to occur more commonly in our patients[43,44,45].

Skin Biopsy was done for 23 patients of them 21 (84%) had features of Scleroderma, Biopsy showed epidermal skin appendages atrophy and collagen fibres in the reticular dermis appear broad and hyalinized. A loss of space between collagen bundles is noted. Mononuclear cells, mostly T cells form a variable perivascular infiltrate in the deep dermis and subcutis.

JOINT INVOLVEMENT

Joint manifestations were seen in 20 of the 25 patients. Small joints involvement was seen more often (52%) similar to South Indian studies[43,44,45]. Major joint involvement is 36.5% . Similar to South Indian study. The incidence of joint involvement was more than Western studies 41%.

5 patients developed deformity with sclerodactyly is similar to South Indian study[44,45,46].

GASTRO INTESTINAL TRACT

Gastro Intestinal involvement was present in 72%, compared to 40.8% South Indian, 50.5% in North Indian, 45% in Western Country studies.

Dysphagia was the commonest symptom, 12 of 25 patients presented with Dysphagia. 6 of 25 patients presented with Regurgitation.

Gastro Intestinal tract involvement was confirmed by Ba swallow and upper gastro dueodenal endoscopy.

Ba swallow showed Dilatation of esophagus in 12 cases who presented with Dysphagia.

Upper Gastro Intestinal endoscopy confirmed gastro esophageal reflux disease who presented with regurgitation.

This Gastro Intestinal involvement was similar to cohen et al and A.N.Malaviya's study[10].

RESPIRATORY SYSTEM INVOLVEMENT:

Exertional Dyspnea with bibasilar crepitations was present for four patients (16%). Owens reported 70% incidence of lung involvement[48]. For all 4 patients chest X ray was taken two of them had normal X ray chest. Another two showed bilateral basal Haziness. For all 4 patients pulmonary function test was done.

For those who showed normal X ray's had mild to moderate restrictive air way disease.

For those who showed bilateral haziness had moderate to severe restrictive airway disease.

Computed tomography was done for all 4 patients. CT chest was normal for whom X ray was normal.

CT showed interstitial lung disease for whom X ray showed bilateral haziness and pulmonary function test showed severe restrictive air way disease.

CARDIOVASCULAR MANIFESTATIONS

Symptoms attributable to cardiovascular system were present in 4 patients (16%). Two of them had ECG changes of T wave abnormality.

Two of them ECG was normal.

Echocardiography showed moderate pericardial effusion for 2 patients and MVP Mitral Valve Prolapse in one patient.

The fourth patient developed moderate pulmonary hypertension secondary to Interstitial Lung Disease (ILD).

Cardiac involvement of 16% is similar to that of South Indian study[43,44,45].

RENAL INVOLVEMENT in the form of significant Proteinuria and systemic hypertension was absent in all cases.

The incidence of renal crisis is found to be low in Indian Population[47].

CONCLUSION

From this study of 25 patients of systemic sclerosis following conclusions were derived.

1. **Female preponderance (Female : Male 11.5 : 1)**
2. **The highest incidence seen in 3rd and 4th decade.**
3. **Limited cutaneous type was commoner than the diffuse SSc.**
4. **Skin and joint manifestations were predominant**
5. **Sclerodactyly and pigmentary changes are more common.**
6. **Raynaud's phenomenon is very much less probably due to climatic causes.**
7. **Fully developed CREST was not present in this study.**
8. **Resorptions of terminal phalanges were less common.**
9. **Gastrointestinal involvement is more than other studies.**
10. **Respiratory involvement was low compared to other studies.**
11. **Cardiac involvement is less like other studies.**
12. **Renal involvement is NIL in this study.**

P

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PROFORMA

I. PARTICULARS OF THE PATIENT

Name : Age : Sex :

Hospital No.: Occupation :

Address :

Chief Complaints:

II. HISTORY OF PROBLEMS: Y/N

HISTORY OF RAYNAUDS PHENOMENON

1. Digital blanching (Pallor) Y/N

   Cyanosis (Blue) Y/N

   Rubor (Red) Y/N
2. Involving one digit Y/N
3. Involving several digits Y/N
4. Symptoms develops sensitivity to cold (Exposure) Y/N
5. Symptoms develops after a stressful condition Y/N
6. Pitting scars in finger tips Y/N
7. Swelling of fingers Y/N
8. Stiffness of fingers Y/N
9. Sclerodactyly Y/N
10. Flexor contracture Y/N
11. Pulp Atrophy Y/N
12. Dry skin Y/N

13. Shiny skin Y/N
14. Loss of hair Y/N
15. Nail fold Thrombi Y/N
16. Digital Infarct Y/N
17. Digital Ulceration Y/N
18. Pseudo clubbing Y/N
19. Skin tightening Y/N
20. Skin Thickening Y/N
21. Shiny appearance Y/N
22. Darkening of skin Y/N
23. Absence of skin wrinkling Y/N
24. Mask like facies Y/N
25. Pinched up nose Y/N
26. Microstomia Y/N
27. Pigmented skin Y/N
28. Depigmented skin (Salt : Pepper apperance) Y/N
29. Telangiectasia Y/N
30. Early Morning stiffness Y/N
31. Fatigue Y/N
32. Musculo articular pain Y/N
33. Arthritis Y/N
34. Arthralgia Y/N

35. Primal muscle weakness Y/N

36. Dry mouth Y/N

37. Hypothermia Y/N

38. Trigeminal neuralgia Y/N

39. Heart burn Y/N

40. Dysphagia Y/N

41. Cough Y/N

42. Dyspnoea Y/N

43. Palpitation Y/N

44. Abd pain Y/N

45. Constipation Y/N

46. Distention Y/N

47. Obstruction Y/N

PAST HISTORY

Hypertension Y/N

Diabetes Mellitus Y/N

Tuberculosis Y/N

Bronchial Asthma Y/N

Chronic Obstructive Pulmonary Diseases Y/N

Heart disease Y/N

Kidney Disease Y/N

Malignancy Y/N

Connective Tissue Disease Y/N

PERSONAL HISTORY

Smoking Y/N

Alcohol Y/N

Tobacco chewing Y/N

Premarital contact Y/N

Extra marital contact Y/N

FAMILY HISTORY

History of similar illness in family Y/N

CLINICAL EXAMINATION

- Conscious
- Oriented
- Temperature
- Anemia
- Clubbing
- Icterus

Lymphadenopathy

- Pulse :
- B.P. :
- R.R. :

FACE

- Mask like facies
- Absence of normal skin wrinkling
- Pinched up nose or beaking of the nose
- Hide bound, Tight skin of face
- Puckered mouth
- Shiny skin
- Pigmented/Depigmented skin
- Telangiectasia

C.V.S.

- S1
- S2
- S3
- Murmur
- Pericardial Rub

R.S.

- N.V.B.S.
- Added sounds
- Crackles
- Rhonchi

- Pleural rub
- Tubular
- Cavernous

P/4

- Soft
- Tenderness
- Hepatomegaly
- Splenomegaly

C.N.S.

FND

URINE ROUTINE EXAMINATION

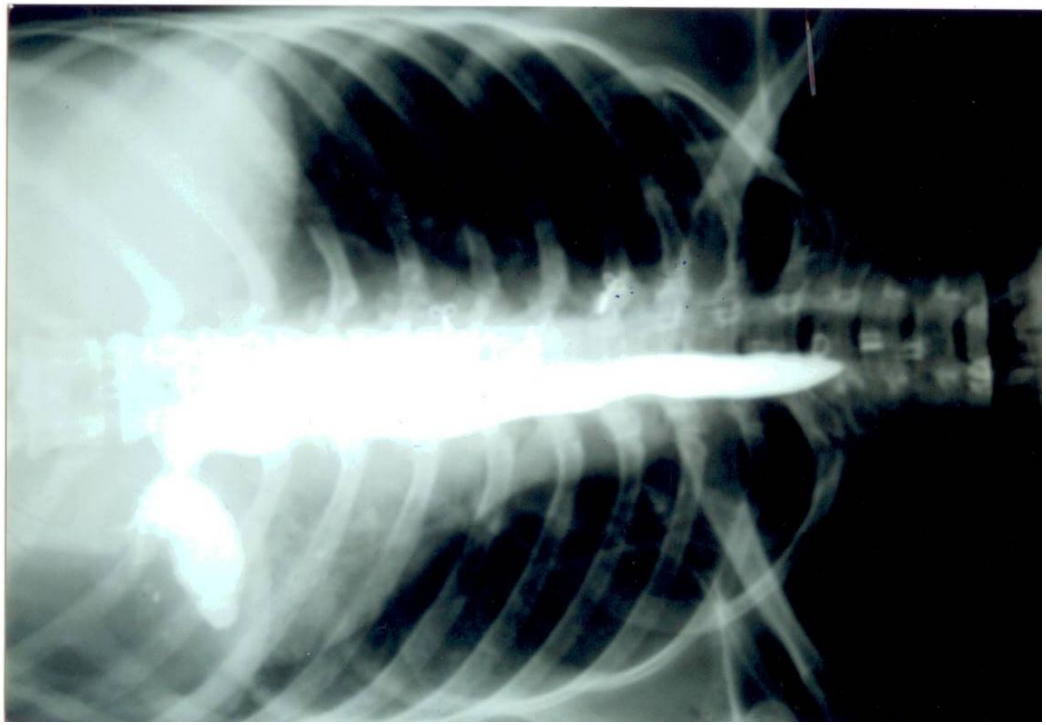
- Albumin
- Sugar
- Deposits

24 hours urine protein

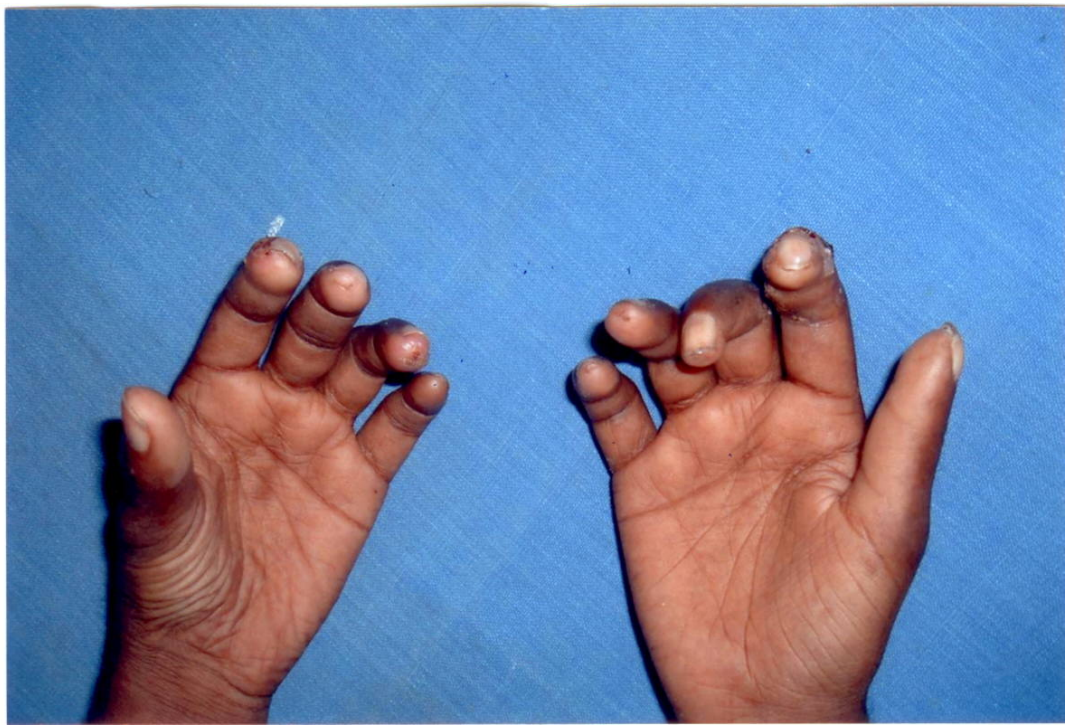
INVESTIGATIONS

1. TC:
2. DC: P_____ L _____ E _____
3. ESR :
4. Hb:
5. Peripheral Blood smear study:
6. Blood sugar
7. Blood urea
8. Serum Creatinine
9. LFT
10. RA Factor
11. ANA :
12. Pulmonary Function Test:
13. X ray chest PA
14. CT Chest
15. ECG
16. Echo
17. Ba Swallow
18. Skin Biopsy

SCLERODERMA FACIES

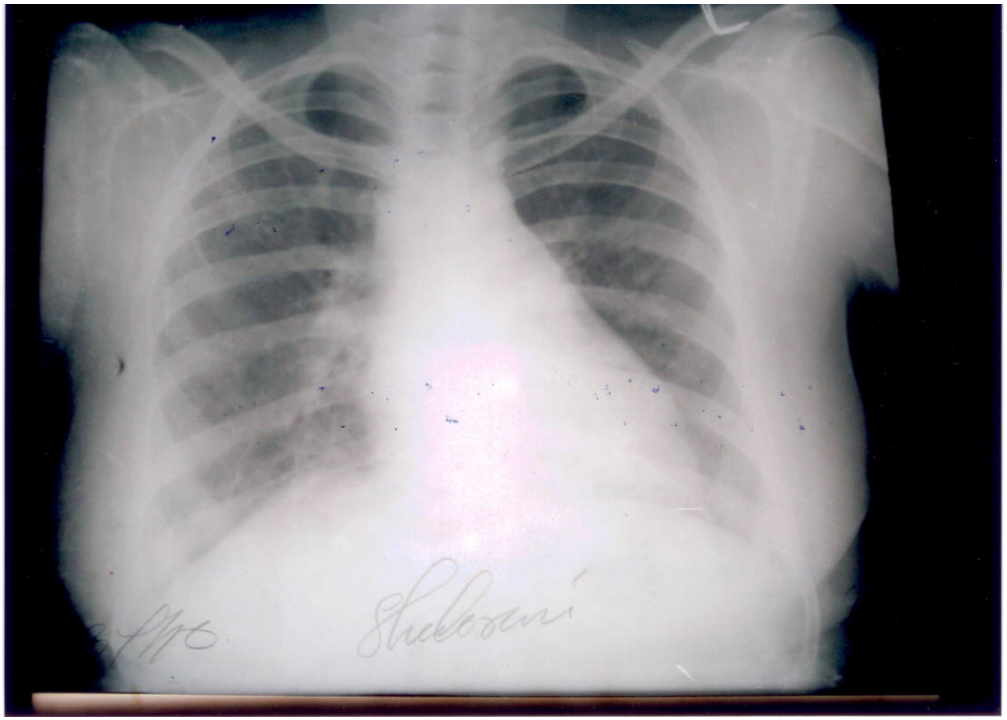


BARIUM SWALLOW SHOWS DILATED ESOPHAGUS



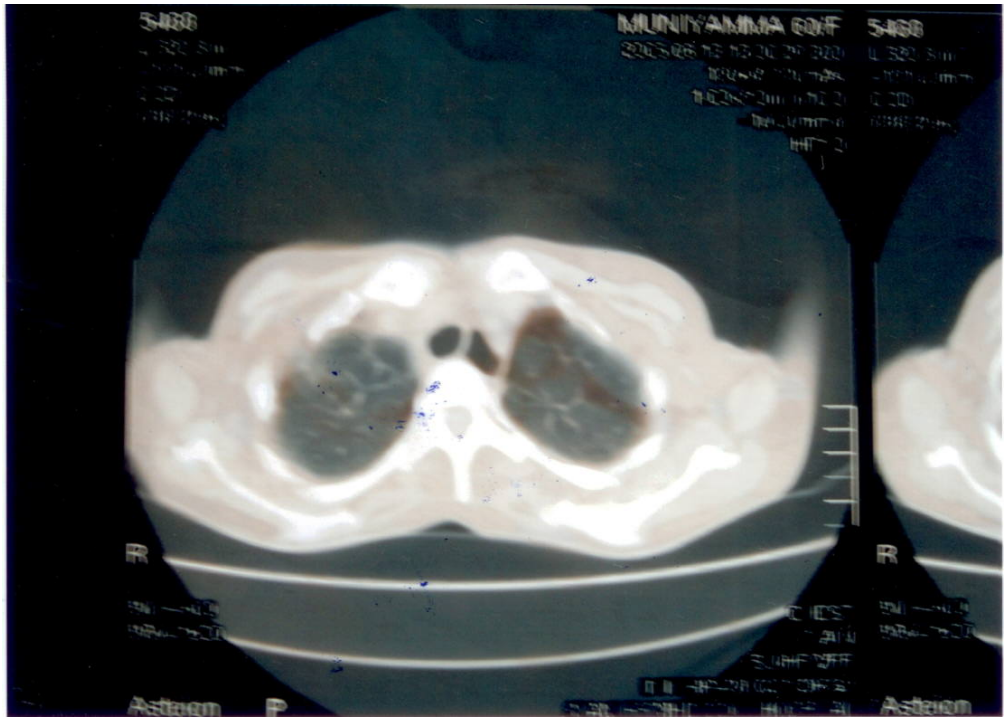
PITTED SCARS ON FINGER TIPS

VASCULITIS ULCER

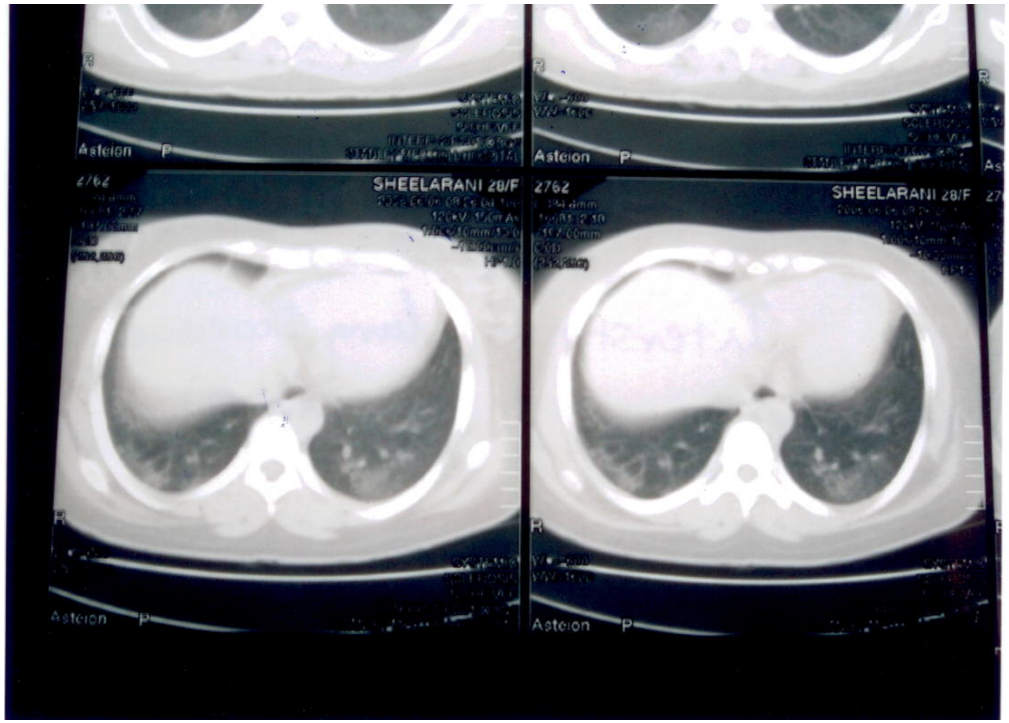


X-RAY CHEST PA VIEW SHOWS BILATERAL BASAL HAZINESS

FRONTAL TEETH APPEAR MORE PROMINENT BECAUSE OF TIGHT PERIORAL SKIN



COMPUTED TOMOGRAPHY – CHEST SHOWS INTERSTITIAL LUNG DISEASE (I.L.D)



COMPUTED TOMOGRAPHY – CHEST SHOWS INTERSTITIAL LUNG DISEASE (I.L.D)

X-RAY HAND RESORPTION

SCLERODACTYLY WITH DEFORMITY

BARIUM SWALLOW SHOWS DILATED ESOPHAGUS